PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
MAYA SKUBATCH
WILSON SONSINI GOODRICH & ROSATI
650 PAGE MILL ROAD
PALO ALTO, CA 94306-1050

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference 12636-305.601	Date of Mailing (*day/month/year*) 20 JUL 2005 FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US04/22367	International filing date (*day/month/year*) 13 July 2004 (13.07.2004)
Applicant SUPERGEN, INC.	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34, chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

   Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90 *bis*.1 and 90 *bis*.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Dewesh Khare Telephone No. (571) 272-1600

Form PCT/ISA/220 (April 2002) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 12636-305.601	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US04/22367	International filing date (*day/month/year*) 13 July 2004 (13.07.2004)	(Earliest) Priority Date (*day/month/year*) 12 September 2003 (12.09.2003)
Applicant SUPERGEN, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
   ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. ____
   ☐ as suggested by the applicant.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.
   ☒ None of the figures

Form PCT/ISA/210 (first sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/22367

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 031/7072; A61K 31/40.
US CL : 514/49, 85, 234.5, 269, 300; 536/23.1, 23.5; 435/69.1, 325; 424/45, 450.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/49, 85, 234.5, 269, 300; 536/23.1, 23.5; 435/69.1, 325; 424/45, 450.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	VONHOFF,D.D. 5-Azacytidine, Annals of Internal Medicine, 1976, 85, Vol. 2, pages 237-245.	1-105
Y	US 4,690,918 (BEPPU et al) 01 September 1987 (01.09.1987), abstract and claims.	1-105

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
26 May 2005 (26.05.2005)

Date of mailing of the international search report
20 JUN 2005

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner of Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
Facsimile No. (703)305-3230

Authorized officer
Devesh Khare
Telephone No. (571) 272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

PCT/US04/22367

Continuation of B. FIELDS SEARCHED Item 3:
CAS online, EAST, Search terms used: decitabine, 5-aza-cytidine, deacetylase inhibitor, trichostatin, leukemia, tumor and DNA methylation inhibitor.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/22367

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

trichostatin compounds (deacetylase inhibitor) have shown activity against resistant phase CML as single agents and were therefore tested in combination.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US04/22367

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:
Claims 1-105 lack an inventive step under PCT Article 33(3) over Von Hoff et al. (Ann. Int. Med. 85(2) pages 237-45, 1976) in view of Beppu et al. (U.S. Patent 4,690,918).

Claims 1-105 are drawn to a method for treating a patient having a disease associated with over-expression of EZH2 (abnormal tyrosine kinase activity) comprising administering a DNA methylation inhibitor and/or a histone deacetylase inhibitor. Additional claim limitations include the histone deacetylase inhibitor such as trichostatin A; DNA methylation inhibitor is a cytidine analog or decitabine (5-azacytidine); administration by intravenous infusion, orally, parenterally, vaginally, via local delivery, or intrathecally.

Von Hoff et al. disclose the use and effectiveness of 5-azacytidine, the cytidine analog, in the treatment of acute myelogenous leukemeia (abstract). It is noted that the applicant discloses in specification on page 1(Field of invention) that the abnormal protein tyrosine kinase activity is associated with chronic myelogenous leukemia (CML).
Von Hoff et al. disclose the effectiveness of 5-azacytidine in childhood leukemia or during the induction phase (page 239, col. 2nd. under European Trials). It is noted that Von Hoff et al. do not provide specific disclosure where the patient's CML is staged prior to administration or the administration is performed when the patient is in blast phase of CML, however Von Hoff et al. disclose that "5-azacytidine seems to be cell-cycle phase specific in that it is most toxic to cells in the S phase, especially at low concentrations" (page 238, first para.). It is also noted that both 5-azacytidine and decitabine which is 5-aza-2'-deoxycytidine (claim 48) have nitrogen in place of the fifth carbon in the base moiety (Von Hoff et al., page 237, 2nd para.). Von Hoff et al. teach the administration of 5-azacytidine by intravenous and subcutaneous routes (page 239, first col. first para. lines 2-7). Von Hoff et al. also suggest the dosage of 5-azacytidine for intravenous administration in the ranges of 1.1-833.0 mg/m^2 (page 239, table 1 and page 240, 2nd col. 2nd para.). Von Hoff et al. disclose the doses from 2 mg/m^2-3.3 mg/m^2 per day and can be increased to 70 to 100 times the initial starting dose (pages 239, last para. through page 240, first para.). Von Hoff et al. further teach the combination therapy of acute myelogenous leukemia with 5-azacytidine with other agents (page 241, table 3). Von Hoff et al. suggest a need for future clinical studies for using 5-azacytidine alone and in combination with other agents in the treatment of acute myelogenous leukemia (page 244, first col. third. para.).Von Hoff et al. differs from the applicant's invention that Von Hoff et al. do not provide an example for the use of histone deacetylase inhibitor such as trichostatin compounds (deacetylase inhibitor).
Beppu et al. disclose the use of trichostatin compounds (deacetylase inhibitor) for treating tumor cells (abstract and claims).

Therefore, one of ordinary skill in the art would have found the applicants claimed method for treating a patient having chronic myelogenous leukemia (CML), with a therapeutically effective amount of a 5-azacytidine (an analog of cytidine or a DNA methylation inhibitor) and/or in combination with deacetylase inhibitor, to have been obvious at the time the invention was made having the above cited references before him. Since Von Hoff et al. teach the use and effectiveness of 5-azacytidine, in the treatment of acute myelogenous leukemeia, and Beppu et al. disclose the use of trichostatin compounds (deacetylase inhibitor) for treating tumor cells , one skilled in the art would have a reasonable expectation for success in combining the teachings of these references to accomplish the treatment of CML because both 5-azacytidine and

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PCT-

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	20 JUL 2005
Applicant's or agent's file reference 12636-305.601	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US04/22367	13 July 2004 (13.07.2004)	12 September 2003 (12.09.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): A61K 031/7072; A61K 31/40. and US CL: 514/49, 85, 234.5, 269, 300; 536/23.1, 23.5; 435/69.1, 325; 424/45, 450.

Applicant

SUPERGEN, INC.

1. This opinion contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Devesh Khare Telephone No. (571) 272-1600

Form PCT/ISA/237 (cover sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/22367

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ in written format

☐ in computer readable form

c. time of filing/furnishing

☐ contained in international application as filed.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/22367

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-105	YES
	Claims NONE	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-105	NO
Industrial applicability (IA)	Claims 1-105	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

Form PCT/ISA/237 (Box No. V) (January 2004)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.